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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate updates to the NCCN Guidelines for Hepatobiliary Cancers into the management of patients with hepatocellular carcinoma, with a focus on systemic therapy
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Hepatobiliary Cancers, with a focus on systemic therapy for hepatocellular carcinoma

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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To view all of the conflicts of interest for the panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Hepatobiliary Cancers, Version 2.2019

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Hepatobiliary Cancers provide treatment recommendations for cancers of the liver, gallbladder, and bile ducts. The NCCN Hepatobiliary Cancers Panel meets at least annually to review comments from reviewers within their institutions, examine relevant new data from publications and abstracts, and reevaluate and update their recommendations. These NCCN Guidelines Insights summarize the panel's discussion and updated recommendations regarding systemic therapy for first-line and subsequent-line treatment of patients with hepatocellular carcinoma.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

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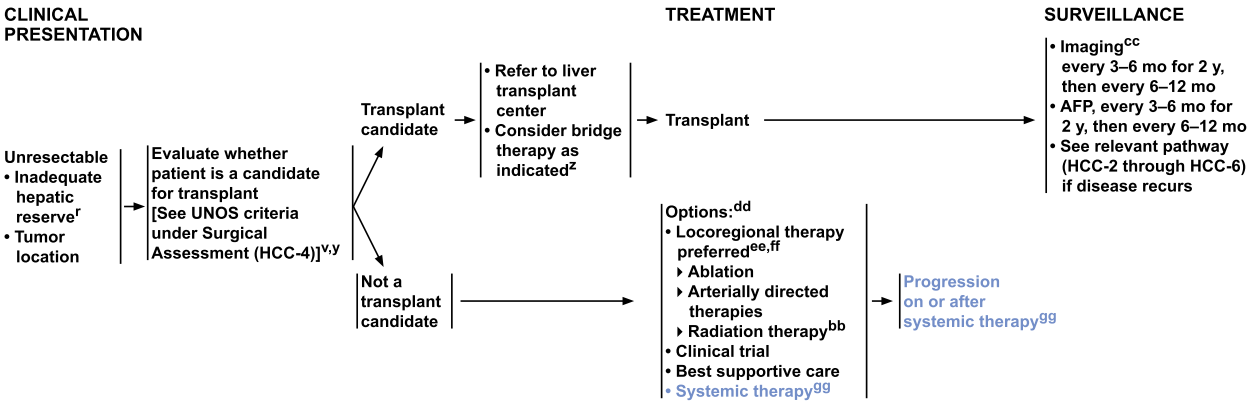


[r]See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[v]See Principles of Surgery (HCC-D).
[y]Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-700.
[z]Many transplant centers consider bridge therapy for transplant candidates. (See Discussion).
[bb]Case series and single-arm studies demonstrate safety and efficacy of radiation therapy in selected cases. See Principles of Locoregional Therapy (HCC-E).
[cc]Multiphasic abdominal/pelvic MRI or multi-phase CT scans for liver assessment are recommended. Consider chest CT. See Principles of Imaging (HCC-A).
[dd]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.
[ee]See Principles of Locoregional Therapy (HCC-E).
[ff]Use of chemoembolization has also been supported by randomized controlled trials in selected populations over best supportive care. (Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-1171) and (Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet 2002;359:1734-1739).
[gg]See Principles of Systemic Therapy (HCC-F).

HCC-5

Overview

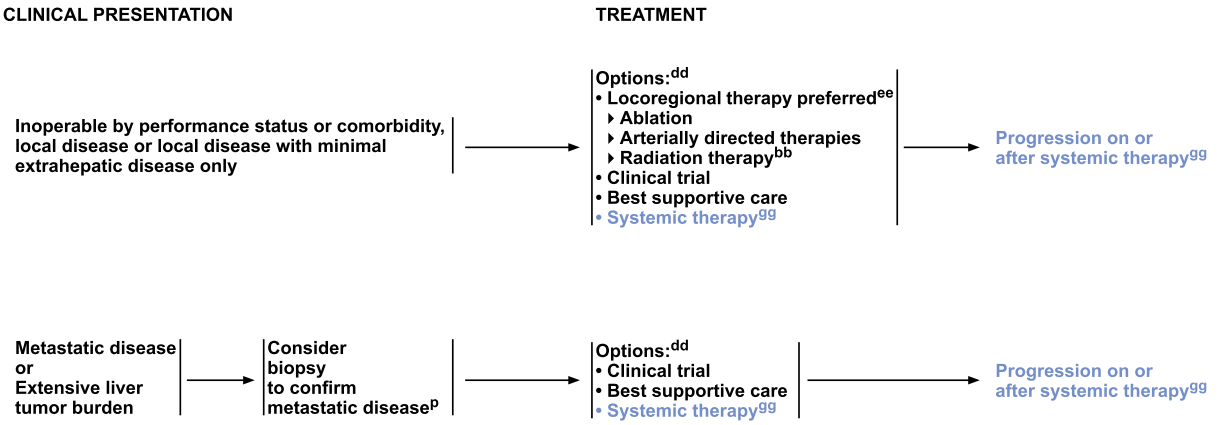
Incidence and mortality rates for cancer overall are declining, but both incidence and mortality rates for hepatocellular carcinoma (HCC) are increasing.[1,2] Risk factors for development of HCC include infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV), and cirrhosis of the liver (eg, alcohol cirrhosis).[3] Metabolic disorders (ie, obesity, diabetes, impaired glucose metabolism, metabolic syndrome, nonalcoholic fatty liver disease [NAFLD]) are associated with increased risk of HCC,[4] and it is anticipated that sequelae of NAFLD, such as nonalcoholic steatohepatitis (ie, a spectrum of conditions characterized by histologic findings of hepatic steatosis with inflammation in individuals who consume little or no alcohol) will replace hepatitis as the most common underlying cause of HCC.[5,6] Other much less common contributors to HCC include Wilson disease, stage IV primary biliary cirrhosis, and inherited errors of metabolism, such as hereditary hemochromatosis, porphyria cutanea tarda, and alpha-1 antitrypsin deficiency.[7]

Management of patients with HCC is complicated by the presence of underlying liver disease. Furthermore, the different etiologies of HCC and their effects on the host liver may impact treatment response and outcome, particularly in an era of improved antiviral therapies. These complexities make treatment decisions in patients with HCC challenging and is the reason multidisciplinary care with the involvement of hepatologists, cross-sectional radiologists, interventional radiologists, transplant surgeons, pathologists, medical oncologists, and surgical oncologists is strongly recommended.[8]

Most patients diagnosed with HCC have advanced disease, and only a small percentage are eligible for potentially curative therapies (see HCC-5, above, and HCC-6, page 305). Furthermore, with the wide range of locoregional therapies available to treat patients with unresectable HCC confined to the liver, systemic therapy has historically often been a treatment of last resort for those with very advanced disease. Until recently, sorafenib has been the only systemic therapy option for patients with advanced disease. However, a number of recent clinical trials have identified one new systemic therapy option for upfront treatment of advanced or unresectable HCC and a number of active agents for HCC that has progressed on or after previous systemic treatment (see HCC-F, page 306).

Sorafenib

Sorafenib, an oral multikinase inhibitor that suppresses tumor cell proliferation and angiogenesis, has been evaluated in 2 randomized, placebo-controlled, phase III



[p]See Principles of Biopsy (HCC-B).
[bb]Case series and single-arm studies demonstrate safety and efficacy of radiation therapy in selected cases. See Principles of Locoregional Therapy (HCC-E).
[dd]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.
[ee]See Principles of Locoregional Therapy (HCC-E).
[gg]See Principles of Systemic Therapy (HCC-F).

HCC-6

trials for the treatment of patients with advanced or metastatic HCC.[9,10]

In the phase III SHARP trial, 602 patients with advanced HCC (defined as those not eligible for or who experienced disease progression after surgical or locoregional therapies) were randomly assigned to sorafenib or best supportive care.[9] Approximately 70% of the patients had macroscopic vascular invasion, extrahepatic spread, or both. Nevertheless, most patients had preserved liver function (≥95% classified as Child-Pugh [C-P] class A) and good performance status (PS; >90% had ECOG PS 0 or 1). Median overall survival (OS) was significantly longer in the sorafenib arm (10.7 months vs 7.9 months for the placebo group; hazard ratio [HR], 0.69; 95% CI, 0.55–0.87; $P<.001$), and 1-year survival rates were 44% for the sorafenib arm and 33% for the placebo arm. Response rate was low, with only 2 patients in the sorafenib arm having a partial response compared with 1 patient in the placebo arm. When taking into account patients with stable disease, the disease control rate was significantly greater in the sorafenib arm compared with the placebo arm (43% vs 32%, respectively; $P=.002$). Sorafenib was well-tolerated, with treatment-related adverse events including diarrhea, weight loss, and hand–foot skin reaction.

In the Asia-Pacific study, which had a similar design to the SHARP study, 226 patients were randomly assigned to the sorafenib or placebo arms (n=150 and n=76, respectively).[10] Although inclusion/exclusion criteria and the percentage of patients with C-P class A liver function (97%) were similar in the Asia-Pacific and SHARP studies, there were significant differences in patient and disease characteristics. Patients enrolled in the Asia-Pacific study were more likely to be younger, have HBV-related disease, have symptomatic disease, and have a higher number of tumor sites than patients in the SHARP study. Although the HR for the sorafenib arm compared with the placebo arm (0.68; CI, 0.50–0.93; $P=.014$) was nearly identical to that reported for the SHARP study, the median OS was strikingly lower in both treatment and placebo groups (6.5 vs 4.2 months).

Results of the subgroup analyses from these studies suggest that sorafenib has impact across a wide spectrum of patients with advanced HCC irrespective of baseline ECOG PS (0–2), tumor burden (presence or absence of macroscopic vascular invasion and/or extrahepatic spread), presence or absence of either lung or lymph node metastasis, tumor stage, prior therapy, and disease etiology (alcohol-related or HCV-related HCC).[11,12] Sorafenib is also an effective treatment irrespective of

PRINCIPLES OF SYSTEMIC THERAPY

- **First-line systemic therapy**
  - **Preferred**
    - **Sorafenib (Child-Pugh Class A [category 1] or B7)[a,b,1,2]**
    - **Lenvatinib (Child-Pugh Class A only)[3]**
  - **Other Recommended**
    - **Systemic Chemotherapy (category 2B)[c]**

- **Subsequent-line therapy if disease progression:**
  - **Regorafenib (Child-Pugh Class A only) (category 1)[d,4]**
  - **Cabozantinib (Child- Pugh Class A only) (category 1)[d,5]**
  - **Ramucirumab (AFP ≥ 400 ng/mL only) (category 1)[d,6]**
  - **Nivolumab (Child-Pugh Class A or B7)[7]**
  - **Sorafenib (Child-Pugh Class A or B7)[a,b] (after first-line lenvatinib[e])**
  - **Pembrolizumab (Child-Pugh Class A only)[8] (category 2B)**

[a]See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[b]Caution: There are limited safety data available for Child-Pugh Class B or C patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, Murry K, Owzar DR, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction:CALGB 60301. J Clin Oncol 2009;27:1800-1805).The impact of sorafenib on patients potentially eligible for transplant is unknown.
[c]There are limited data supporting the use of FOLFOX, and use of chemotherapy in the context of a clinical trial is preferred. (Qin S, Bai Y, Lim HY, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol. 2013;31:3501-3508.)
[d]The data reflect use on or after sorafenib.
[e]There are no data to define optimal treatment for those who progress after lenvatinib, nor for the use of lenvatinib after sorafenib.

HCC-F
1 OF 2

serum concentrations of alanine aminotransferase/aspartate aminotransferase/alpha fetoprotein (AFP) and total bilirubin levels.[12,13] Ultimately, however, it has been up to the patient and physician to determine whether the survival differences between the treatment and placebo groups in the SHARP[11] and Asia-Pacific[10] studies (2.8 and 2.3 months, respectively) are clinically meaningful enough to use the treatment.

Data on the efficacy of sorafenib in patients with C-P class B liver function are limited because only patients with preserved liver function (C-P class A) were to be included in those trials.[14] However, approximately 28% of the 137 patients enrolled in a phase II trial evaluating sorafenib in the treatment of HCC had C-P class B liver function.[15] A subgroup analysis of these patients showed a median OS of only 3.2 months for those in the C-P class B group compared with 9.5 months for the C-P class A group.[16] Other investigators have also reported lower median OS for patients with C-P class B liver function.[17–21] In the GIDEON registry, the safety profile of sorafenib was generally similar for C-P classes A and B, although OS was shorter in patients with C-P class B liver function.[20] In the final analysis of the trial, in the intent-to-treat population (n=3,213), median OS was 13.6 months for the C-P class A group compared with 5.2 months for the C-P class B group[22]; time to progression (TTP) was, however, similar for the 2 groups (4.7 and 4.4 months, respectively). These unsurprising results reflect the balance between cancer progression and worsening liver disease as competing causes of death for patients with unresectable HCC, and forms the basis for excluding patients with poorer liver function from these and other clinical trials.

In addition to clinical outcome, impaired liver function may impact the dosing and toxicity of sorafenib. Abou-Alfa et al[16] found higher levels of hyperbilirubinemia, encephalopathy, and ascites in patients with C-P class B liver function, although it is difficult to separate the extent to which treatment drug and underlying liver function contributed to these disease manifestations. A pharmacokinetic and phase I study of sorafenib in patients with hepatic and renal dysfunction showed an association between elevated bilirubin levels and possible hepatic toxicity.[23] Finally, it is important to mention that sorafenib induces only rare objective volumetric tumor responses,[14] which has led to a search for other validated criteria to evaluate tumor response (such as RECIST[24] or EASL criteria[25]).

Sorafenib is recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for

patients who have unresectable HCC and are not a transplant candidate; those who are inoperable based on PS or comorbidity or who have local disease or local disease with minimal extrahepatic disease only; and those with metastatic HCC or extensive liver tumor burden. Based on results of the SHARP and Asia-Pacific studies, sorafenib is a category 1 recommendation for first-line therapy in patients with C-P class A liver function and a category 2A recommendation for those with C-P class B7 liver function.

Lenvatinib

Lenvatinib is an inhibitor of VEGF, fibroblast growth factor, PDFG, and other growth signaling targets. In the randomized, noninferiority phase III REFLECT trial, patients with unresectable HCC (N=954) were randomized to receive either lenvatinib or sorafenib as first-line treatment.[26] The trial was designed to demonstrate noninferiority rather than superiority of lenvatinib, which was demonstrated with an OS of 13.6 months in the lenvatinib arm compared with 12.3 months for sorafenib (HR, 0.92; 95% CI, 0.79–1.06). Based on results of this trial, the FDA approved lenvatinib in 2018 as first-line treatment for patients with unresectable HCC. First-line lenvatinib is included as an option in the NCCN Guidelines for patients who have unresectable HCC and are not a transplant candidate; those who are inoperable based on PS or comorbidity, or who have local disease or local disease with minimal extrahepatic disease only; and those with metastatic HCC or extensive liver tumor burden. Lenvatinib is recommended for patients with C-P class A liver function only. However, the panel voted to make it a category 2A recommendation rather than category 1 because the study was open-label (which could have biased the time to treatment changes) and because it excluded patients with major portal vein involvement.

Subsequent-Line Therapy if Disease Progression

Until recently, despite a series of randomized trials, no subsequent-line systemic therapy options have been available for patients with HCC who experience disease progression on or after sorafenib. The randomized, double-blind, placebo-controlled, international phase III RESORCE trial assessed the efficacy and safety of regorafenib in 573 patients with HCC and C-P class A liver function whose disease progressed on sorafenib.[27] Compared with placebo (median survival, 7.8 months), regorafenib (median survival, 10.6 months) improved OS (HR, 0.63; 95% CI, 0.50–0.79; $P<.001$), progression-free survival (PFS; HR, 0.46; 95% CI, 0.37–0.56; $P<.001$), TTP (HR, 0.44; 95% CI, 0.36–0.55; $P<.001$), objective response (11% vs 4%; $P=.005$), and disease control (65% vs 36%; $P<.001$). Adverse events were universal among patients who received regorafenib (n=374), with the most frequent grade 3 or 4 treatment-related adverse events being hypertension (15%), hand-foot skin reaction (13%), fatigue (9%), and diarrhea (3%). The 7 deaths that occurred were considered by the investigators to have been related to treatment with regorafenib. Based on results of this trial, the FDA approved regorafenib in 2017 for patients with HCC whose disease progressed on or after sorafenib, and the NCCN Guidelines included regorafenib as a category 1 option for patients with C-P class A liver function who experience disease progression on or after sorafenib.

Cabozantinib, a tyrosine kinase inhibitor, was assessed in the randomized phase III CELESTIAL trial including 707 patients with incurable HCC whose disease had progressed on or after sorafenib, with 7.6% of the sample having received more than one line of previous treatment.[28] Median OS and PFS were significantly greater in patients randomized to receive cabozantinib (OS: 10.2 and 5.2 months, respectively; HR, 0.76; 95% CI, 0.63–0.92; $P=.005$) compared with placebo (PFS: 8.0 and 1.9 months, respectively; HR, 0.44; 95% CI, 0.36–0.52; $P<.001$). Although the objective response rate was better in the cabozantinib arm than in the placebo arm ($P=.009$), this value was low, with a partial response reported in only 4% of patients who received cabozantinib (vs 0.4% of those who received placebo). Cabozantinib was FDA-approved in 2019 for patients with C-P class A liver function who have disease progression on or after sorafenib and is a category 1 option in the current NCCN Guidelines.

In the randomized phase III REACH trial, the VEGF receptor inhibitor ramucirumab was assessed as second-line therapy following sorafenib in patients with advanced HCC (N=565).[29,30] Although this regimen did not improve OS, median PFS (HR, 0.63; 95% CI, 0.52–0.75; $P<.001$) and TTP (HR, 0.59; 95% CI, 0.49–0.72; $P<.001$) were improved, relative to the placebo group. However, a subgroup analysis showed that, for patients with a baseline AFP level of ≥400 ng/mL (n=250), OS and PFS were 7.8 and 2.7 months, respectively, in the ramucirumab arm, and 4.2 and 1.5 months, respectively, in the placebo arm. Analyses of patient-focused outcomes showed that deterioration of symptoms was not significantly different in patients randomized to receive ramucirumab compared with placebo.[30]

Based on these findings, the randomized phase III REACH-2 trial assessed the efficacy of ramucirumab in patients with HCC who had disease progression on or after sorafenib and had a baseline AFP level of ≥400 ng/mL (N=292).[31] OS and PFS were greater in patients who received ramucirumab and best supportive care compared with placebo and best supportive care (median OS, 8.5 vs 7.3 months, respectively; HR, 0.71; 95% CI, 0.53–0.95; $P=.20$; median PFS, 2.8 vs 1.6 months, respectively; HR, 0.45; 95% CI, 0.34–0.60; $P<.001$). A pooled analysis of results from REACH and REACH-2, including 542 patients with disease progression on or after

sorafenib who had a baseline AFP level of ≥400 ng/mL, showed that median OS was greater for those who received ramucirumab compared with placebo (8.1 vs 5.0 months, respectively; HR, 0.69; 95% CI, 0.57–0.84; $P<.001$).[32] Based on these results, ramucirumab is recommended by the NCCN panel as a category 1 option for patients with a baseline AFP level of ≥400 ng/mL who have disease progression on or after systemic sorafenib.

Nivolumab, an anti–PD-1 antibody, was assessed in the nonrandomized, multi-institutional phase I/II CheckMate 040 trial that included 48 patients with advanced HCC in a dose-escalation phase and 214 patients in a dose-expansion phase.[33] Among patients treated with 3 mg/kg of nivolumab, the objective response rate was 20% for those in the dose-expansion phase and 15% for those in the dose-escalation phase. Disease control rates were 64% and 58% for patients in these phases, respectively. The 9-month OS rate for patients in the dose-expansion phase was 74%. In the dose-escalation phase, 25% of patients had grade 3 or 4 treatment-related adverse events. In the dose-expansion phase, analyses of 57 patients without viral hepatitis whose disease progressed following sorafenib showed a disease control rate of 61%. Median OS and 6-month OS rates for these patients were 13.2 months and 75%, respectively. Additional analyses from this trial showed a median duration of response of 17 months in patients who were sorafenib-naïve (n=80) and 19 months in those who had been previously treated with sorafenib (n=182); 18-month OS rates for these patients were 57% and 44%, respectively.[34] Based on results of the CheckMate 040 trial,[33] the FDA approved nivolumab in 2017 for patients with HCC whose disease progressed on or after sorafenib, and the NCCN panel recommends nivolumab for patients with disease progression on or following systemic therapy and with C-P class A or B7 liver function. CheckMate 459, the randomized controlled phase III trial comparing nivolumab with sorafenib as first-line treatment in patients with advanced HCC, has been fully enrolled and results are awaited (ClinicalTrials.gov identifier: NCT02576509).

Pembrolizumab, another anti–PD-1 antibody, was assessed in the nonrandomized, open-label, phase II KEYNOTE-224 trial, which included 104 patients with HCC whose disease progressed on or who were intolerant of sorafenib.[35] Approximately 17% of patients had an objective response (all partial responses, except for 1 patient who had a complete response), 44% had stable disease, and 33% had progressive disease. Median duration of response was not reached, and at the time of publication, assessment was ongoing in 12 of the 18 responders. The safety profile was similar to that seen for this drug in other tumor types. Based on these results, the FDA granted accelerated approval for pembrolizumab in patients with HCC who were previously treated with sorafenib. However, the phase III KEYNOTE-240 trial comparing pembrolizumab and placebo in the second-line treatment of HCC did not meet its primary end points (OS and PFS), although results were consistent with those from the phase II trial and PFS trended in favor of pembrolizumab.[36] Based on the reported results, the panel changed the recommendation for pembrolizumab from category 2A to category 2B for patients with C-P class A liver function and disease progression following systemic therapy. The full dataset from the phase III trial will be reviewed when available.

These subsequent-line therapy options have been studied after sorafenib failure, and ramucirumab has been studied in patients with high AFP levels. The relatively rapid development of these numerous treatment options has made it difficult to address the important question of sequencing them, other than for those that have been approved for use in patients with disease progression on or following sorafenib. Sorafenib may be used in patients with disease progression on or following first-line lenvatinib (C-P class A or B7 liver function only), but currently no data support the use of lenvatinib in patients with disease progression after sorafenib.

Other Agents and Emerging Therapies

FOLFOX4 (oxaliplatin, infusional fluorouracil, and leucovorin) was compared with doxorubicin in a phase III trial including 371 Asian patients with advanced HCC.[37] The primary OS end point was not met, but PFS was greater for FOLFOX4 compared with doxorubicin (HR, 0.62; 95% CI, 0.49–0.79; $P<.001$). Subgroup analyses from this trial including patients from China (n=279) showed both an OS and a PFS benefit for FOLFOX4 compared with doxorubicin (HR, 0.74; 95% CI, 0.55–0.98; $P=.03$, and HR, 0.55; 95% CI, 0.45–0.78; $P<.001$, respectively), with median OS and PFS of 5.7 and 2.4 months, respectively, for patients randomized to receive FOLFOX4, and 4.3 and 1.7 months, respectively, for those randomized to receive doxorubicin.[38] Although none of the patients in this sample experienced a complete response, 8.6% who received FOLFOX4 had a partial response compared with 1.4% who received doxorubicin ($P=.006$). The NCCN panel recommends FOLFOX as a category 2B option for first-line systemic therapy for patients with unresectable or advanced HCC, because concern regarding the control arm used in this study (doxorubicin) led to less consensus among the panel.

Bevacizumab, another VEGF receptor inhibitor, has modest clinical activity (as a single agent or in combination with other systemic therapy options) in phase II studies in patients with advanced HCC.[39–43] Bevacizumab + atezolizumab is being assessed as a first-line treatment option for patients with unresectable or metastatic HCC in a phase Ib trial.[44] Analyses from an independent

reviewer (using HCC mRECIST criteria) of 73 patients showed an overall response rate of 34% (11% complete response, 23% partial response), with stable disease in 41% of patients and progressive disease in 19%. Duration of response was 40% for ≥6 months and 20% for ≥12 months. Although these results are promising, results of an ongoing randomized trial are awaited to make a determination on this combination therapy (ClinicalTrials.gov identifier: NCT03434379).

In a phase III trial, linifanib, a VEGF and PDFG receptor inhibitor, was compared with sorafenib in patients with advanced HCC (N=1,035).[45] Those who were randomized to receive linifanib had a greater objective response rate (P=.018), but also a greater rate of serious adverse events (P<.001) and adverse events leading to dose reduction and drug discontinuation (P<.001) compared with patients randomized to receive sorafenib. Overall, survival did not significantly differ between the drugs.

Data from a phase II trial have demonstrated potential activity and tolerability of axitinib as second-line therapy in patients with intermediate/advanced HCC with C-P class A liver function.[46] Additional data are needed before this regimen is recommended in the NCCN Guidelines for the treatment of patients with HCC.

Summary

Treatment of HCC often necessitates multidisciplinary care. Until recently, sorafenib has been the only systemic therapy option for patients with advanced disease. However, research on systemic therapy options for patients with advanced HCC has moved forward quickly. Lenvatinib is now a first-line option for patients with HCC, whereas a number of agents have recently been added to the NCCN Guidelines for subsequent-line therapy in patients with disease progression, including regorafenib, cabozantinib, ramucirumab, nivolumab, and pembrolizumab. Second-line therapies following lenvatinib have not been studied. Additional agents for HCC treatment are under investigation.

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